Article

Identification of crucial metabolites/reactions in tumor signaling networks

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Abstract

Changes in metabolites/reactions of cell signaling pathways play a key role in tumorigenesis. In present study, betweenness centrality, degree and *k*-core value of every metabolite/reaction in tumor signaling pathways p53, AKT, Ras, JAK-STAT, TNF, and VEGF were calculated. Crucial metabolites/reactions in these tumor signaling networks were identified using betweenness centrality. The p53-P-P was identified as the most important metabolite/reaction in p53 signaling pathway, followed by (Ac-p53-P)2 and DNA damage; Akt is the most important metabolite/reaction in AKT signaling pathway, followed by PI3K and PIP3; Ras-GTP is the most important metabolite/reaction in TNF signaling pathway, followed by MEKK1, JNKK and Ras-GDP. The *k*-core analysis showed that VEGF signaling pathway is the most compact network among these signaling pathways.

Keywords tumor; signaling pathway; crucial metabolite/reaction; *k*-core analysis; betweenness centrality.

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1 Introduction

Changes in metabolites/reactions of cell signaling pathways play a key role in tumorigenesis. A large number of ligands, receptors, signaling proteins and links exist in the signaling pathways of a human cell. Complex signaling pathways form various metabolic networks and affect the metabolic processes of tumors.

Tumor signaling pathways of the human body include mainly JAK-STAT signaling pathway (Marrero, 2005), p53 signaling pathway (Himes et al., 2006; Ho et al, 2006), NF-κB signaling pathway, Ras, PI3K and mTOR signaling pathway (Kolch, 2002; Stauffer et al., 2005), Wnt NF-κB signaling pathway (Katoh, 2005) and BMP signaling pathway (Moustakas, 2002), etc. Various ligands, receptors and signaling proteins are associating with these signaling pathways. They form a complex and directed network, similar to the various networks reported (Ibrahim et al., 2011; Huang and Zhang, 2012; Zhang, 2012a).

Previous studies of tumor signaling pathways focus mainly on the metabolic processes and chemical

processes of some selected metabolites, and the tumorigenesis induced by abnormal signaling from mutation of this metabolite or gene. Detailed studies were also conducted on the chemical structure and the metabolic pathways of ligands, receptors, and signaling proteins. A most recent study on network analysis of tumor signaling networks was the degree distribution analysis of tumor signaling networks (Huang and Zhang, 2012). In their study, Huang and Zhang (2012) considered that the metabolites/reactions (steps) with higher degree are often crucial metabolites/reactions.

Although a tumor signaling pathway may be very complex, some metabolites/reactions in the network are more important for tumorigenesis than the remaining metabolites/reactions. Using network analysis methods, the present study will identify crucial metabolites/reactions of some important tumor signaling pathways, aiming to provide valuable clues for further studies.

2 Material and Methods

2.1 Data sources

Six tumor signaling pathways are closely related to various metabolites/reactions (Huang and Zhang, 2012). The later were collated and interpreted to form a new analytical database. All image information for signaling networks were downloaded from SABiosciences (http://www.sabiosciences.com/pathwaycentral.php) (Pathway Central, 2012) and Abcam (http://www.abcam.com/) (Abcam, 2012).

2.2 Data conversion

Each metabolite/reaction (node) in the tumor signaling image was given an ID number to generate a network. Open Data/Data editors/Matrix editor in the UCINET software, and then paste the network data into the matrix editor. After that we saved the network data as a file in ".##h" format. In the NetDraw program, we choose the File/Open/Ucinet dataset/Network and open the ".##h" file, and then choose File/Save data as/Pajek/Net file to save it as a file in ".net" format (Kuang and Zhang, 2011). Through this step, all tumor signaling images were interpreted as the network data used in Pajek.

2.3 Software and methods

2.3.1 UCINET

The UCINET software on network analysis integrated the NetDraw, a program for one- and two-dimensional network analysis, and the ongoing three-dimensional display application, Mage, etc. It also integrated some application programs of Pajek that used in large-scale network analysis. The UCINET software can read text files, KrackPlot, Pajek, Negopy, and VNA files. It can handle the networks as large as 32767 nodes.

2.3.2 Pajek

Pajek is the large and complex software for network analysis, which is characterized by quick computing, higher degree of visualization and abstraction. It can handle the networks with millions of nodes. Pajek provides abstract methods for handling complex networks, and is mainly used in analyzing the global structure of networks.

Degree

Degree is the most basic property of a complex network (Kuang and Zhang, 2011; Huang and Zhang, 2012; Zhang, 2012a, b). The degree of a node is defined as the number of its connected nodes. In a sense, the larger the degree of a node, the more important the node is (Zhang, 2012a, b). In a directed network, the degree is the sum of incoming degree and outgoing degree. Choosing In/Out/All commands of Net/Partitions/Degree menu in Pajek, the degree, incoming degree and outgoing degree will be calculated.

Betweenness centrality

Betweenness centrality is the measure of a node's centrality in a network (Zhang, 2012a, b). It is equal to the number of shortest paths from all nodes to all others that pass through that node. In general, betweenness

centrality is a more useful measure than degree in identifying the importance of a node. For a network, betweenness centrality is more global than degree.

k-neighbor and k-core network

If the node *i* and node *j* are connected with an edge, then the two nodes are neighbors. If the node *i* connects to node *j* by going through *k* edges, then two nodes are called *k*-nearest neighbor (*k*-neighbor) for each other. For a directed graph, there are two types of *k*-nearest neighbors, *k*-out and -in nearest neighbors. Starting from the node *i*, if there are *k* positive-directed edges between nodes *i* and *j*, and *j* is called the *k*-out nearest neighbor of *i* and, *i* is called the *k*-in nearest neighbor of *j*. For a directed graph, choose Net/k-Neighbors/Output in Pajek, and input the longest distance *k* value in the pop-up dialog box (*k*=0 means finding all *k*-neighbors of the node). The result is a partition file, in which the ID number of the class that node *i* belongs to is the shortest path from required node to node *i*. In addition, choosing Net/k-Neighbors/All in Pajek, will output the *k*-neighbors of nodes for an undirected graph.

In a network, if any node has at least *k* neighbors that belong to the network, the network is called a *k*-core network. To find the core of a complex network means finding all *k*-core networks in the complex network. A large total *k*-core value means a compact network.

3 Results

3.1 p53 signaling pathway

The image of p53 signaling pathway is shown in Fig. 1.

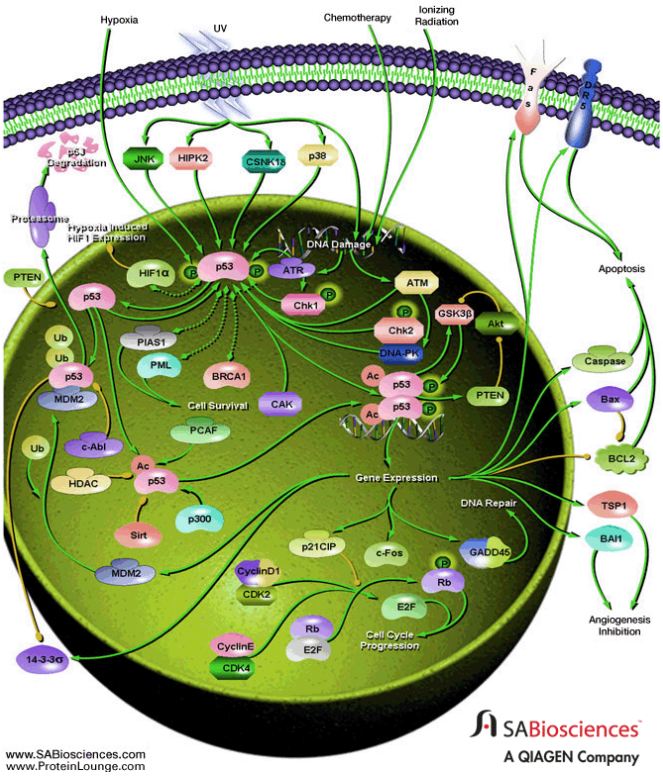

Fig. 1 P53 signaling pathway (Pathway Central, 2012)

Using Netdraw, the network graph of P53 signaling pathway in Fig. 1 was drawn, as indicated in Fig. 2.

Fig. 2 The network graph of p53 signaling pathway.

Table 1 Degree of metabolites/reactions in p53 signaling pathway.

Metabolites/ reactions	Degree	Metabolites/ reactions	Degree	Metabolites/ reactions	Degree	Metabolites/ reactions	Degree
Hypoxia	1	p38	2	HDAC	1	E2F	3
UV	5	BRCA1	1	DNA-PK	2	Rb-E2F	1
Chemotherapy	1	PTEN	3	Akt	2	CyclinD1-CDK2	1
ATM	3	PML	1	Chk2-P	1	CyclinE-CDK4	1
DNA damage	5	proceasome	2	GSK3β	2	BAI1	1
lonizing Radiation	1	PIAS1	1	p21CIP	2	Fas	1
ART	3	c-Abl	1	Caspase	1	DR5	1
JNK	2	PCAF	1	c-Fos	1	Gene Expression	12
Chk1-P	2	Ub	1	Bax	2	(Ac-p53-P)2	5
HIPK2	2	p300	1	GADD45	1	Ac-p53	6
HIFα	1	MDM2	2	BCL2	3	Ub-Ub-p53-MDM2	6
CSNK1	2	Sirt	1	Rb-P	3	p53	2
CAK	1	14-3-3θ	2	TSP1	1	p53-P-P	18

Counted degree of metabolites/reactions is listed in Table 1.

Use Pajek/Net/Partitions/Core/All to calculate all *k*-core networks of p53 signaling pathway. The result is a partition file, in which the ID number of the class that node *i* belongs to is the largest *k* value of all *k*-core networks of node *i*. The results showed that *k*-core value of UV, ATM, DNA damage, ART, JNK, Chk1-P, HIPK2, CSNK1, p38, PTEN, proceasome, MDM2, 14-3-3θ, DNA-PK, Akt, GSK3β, Bax, BCL2 Gene, Expression, (Ac-p53-P)2, Ub-Ub-p53-MDM2, and p53-P-P is 2, and *k*-core value is 1 for remaining metabolites/reactions.

Use Pajek/Vector/Centrality/Betweeness to calculate the betweenness centrality of p53 signaling pathway.

The results are listed in Table 2. A larger betweenness centrality means that the corresponding metabolite/reaction is more crucial in the signaling pathway. Thus, p53-P-P is identified as the most important metabolite/reaction in p53 signaling pathway, followed by (Ac-p53-P)2, DNA damage, and ATM.

Table 2 Betweenness centrality (BC) of metabolites/reactions in p53 signaling pathway.

Metabolites/ reactions	BC	Metabolites/ reactions	BC	Metabolites/ reactions	BC	Metabolites/ reactions	BC
Hypoxia	0	p38	0.000392	HDAC	0	E2F	0.001569
UV	0	BRCA1	0	DNA-PK	0	Rb-E2F	0
Chemotherapy	0	PTEN	0	Akt	0.000392	CyclinD1-CDK2	0
ATM	0.004706	PML	0	Chk2-P	0	CyclinE-CDK4	0
DNA damage	0.005098	proceasome	0.000392	GSK3β	0.001569	BAI1	0
lonizing Radiation	0	PIAS1	0	p21CIP	0	Fas	0
ART	0	c-Abl	0	Caspase	0	DR5	0
JNK	0.000392	PCAF	0	c-Fos	0	Gene Expression	0
Chk1-P	0	Ub	0	Bax	0	(Ac-p53-P)2	0.00549
HIPK2	0.000392	p300	0	GADD45	0	Ac-p53	0.001961
HIFα	0	MDM2	0	BCL2	0.001569	Ub-Ub-p53-MDM2	0
CSNK1	0.000392	Sirt	0	Rb-P	0.001569	p53	0
CAK	0	14-3-3θ	0	TSP1	0	p53-P-P	0.024314

3.2 AKT signaling pathway

Fig. 3 is the network graph of AKT signaling pathway.

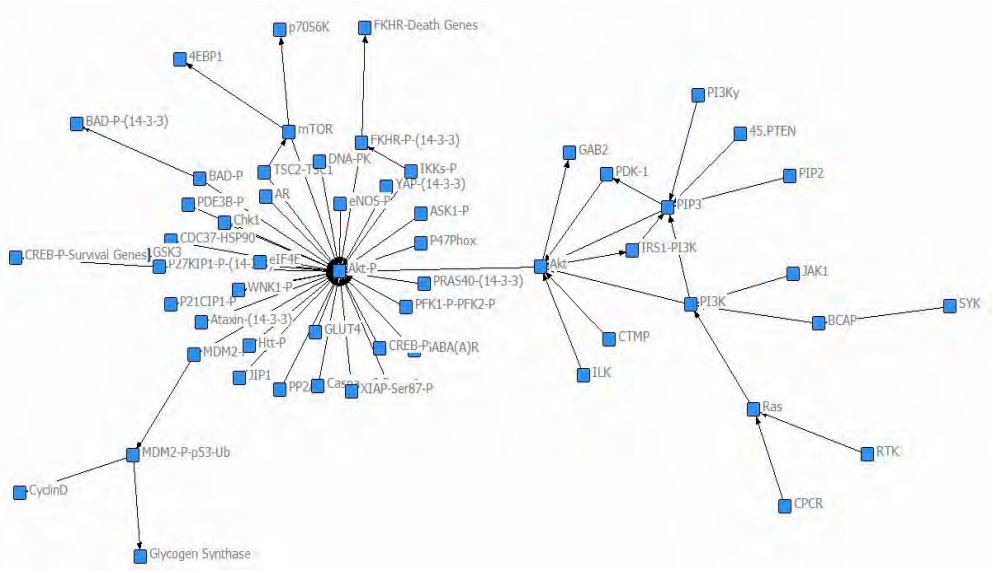

Fig. 3 The network graph of AKT signaling pathway.

Table 3 Degree of metabolites/reactions in AKT signaling pathway.

Metabolites/ reactions	Degree	Metabolites/ reactions	Degree	Metabolites/ reactions	Degree	Metabolites/ reactions	Degree
GABA(A)R	1	Raf1	1	GSK3	1	JAK1	1
CPCR	1	Caspase9-P	1	CREB-P-Survival Genes	1	BCAP	1
Ras	3	XIAP-Ser87-P	1	CyclinD	1	PI3Ky	2
PI3K	5	PDE3B-P	1	FKHR-P-(14-3-3)	1	GLUT4	1
GAB2	1	BAD-P	2	Glycogen Synthase	3	Akt	1
RTK	1	TSC2-TSC1	2	FKHR-Death Genes	1	Akt-P	8
ILK	1	BAD-P-(14-3-3)	1	PFK1-P-PFK2-P	1	JIP1	33
PIP2	1	mTOR	4	YAP-(14-3-3)	1	ASK1-P	1
SYK	1	Chk1	1	IKKs-P	1	4EBP1	1
IRS1-PI3K	2	p70S6K	1	Ataxin-(14-3-3)	2	eIF4E	1
CTMP	1	P21CIP1-P	1	Htt-P	1	AR	1
PIP3	7	MDM2-P	2	P47Phox	1	DNA-PK	1
PP2A	1	P27KIP1-P-(14-3-3)	2	WNK1-P	1	eNOS-P	1
PDK-1	2	MDM2-P-p53-Ub	3	PRAS40-(14-3-3)	1		
CDC37-HSP90	1	CREB-P	3	45.PTEN	1		

Table 4 Betweenness centrality (BC) of metabolites/reactions in AKT signaling pathway.

Metabolites/ reactions	BC	Metabolites/ reactions	BC	Metabolites/ reactions	BC	Metabolites/ reactions	BC
GABA(A)R	0	Raf1	0	GSK3	0	JAK1	0
CPCR	0	Caspase9-P	0	CREB-P-Survival Genes	0	BCAP	0.002193
Ras	0.004386	XIAP-Ser87-P	0	CyclinD	0	PI3Ky	0
PI3K	0.01127	PDE3B-P	0	FKHR-P-(14-3-3)	0.000313	GLUT4	0
GAB2	0	BAD-P	0	Glycogen	0	Akt	0.015351
RTK	0	TSC2-TSC1	0	FKHR-Death	0	Akt-P	0
ILK	0	BAD-P-(14-3-3)	0	PFK1-P-PFK2-P	0	JIP1	0
PIP2	0	mTOR	0.000627	YAP-(14-3-3)	0	ASK1-P	0
SYK	0	Chk1	0	IKKs-P	0	4EBP1	0
IRS1-PI3K	0.00219	p70S6K	0	Ataxin-(14-3-3)	0	eIF4E	0
CTMP	0	P21CIP1-P	0	Htt-P	0	AR	0
PIP3	0.00908	MDM2-P	0	P47Phox	0	DNA-PK	0
PP2A	0	P27KIP1-P-(14-3-3)	0	WNK1-P	0	eNOS-P	0
PDK-1	0	MDM2-P-p53-Ub	0.000627	PRAS40-(14-3-3)	0		
CDC37-HSP90	0	CREB-P	0	45.PTEN	0		

Counted degree of metabolites/reactions is listed in Table 3.

The results showed that *k*-core value of FKHR-P-(14-3-3), IKKs-P, Akt, Akt-P, mTOR, TSC2-TSC1, PDK-1, PIP3, IRS1-PI3K, and PI3K is 2, and *k*-core value is 1 for remaining metabolites/reactions.

Betweenness centrality of metabolites/reactions showed that Akt is the most important metabolite/reaction in AKT signaling pathway, followed by PI3K and PIP3 (Table 4).

3.3 JAK-STAT signaling pathway

Fig. 4 is the network graph of JAK-STAT signaling pathway.

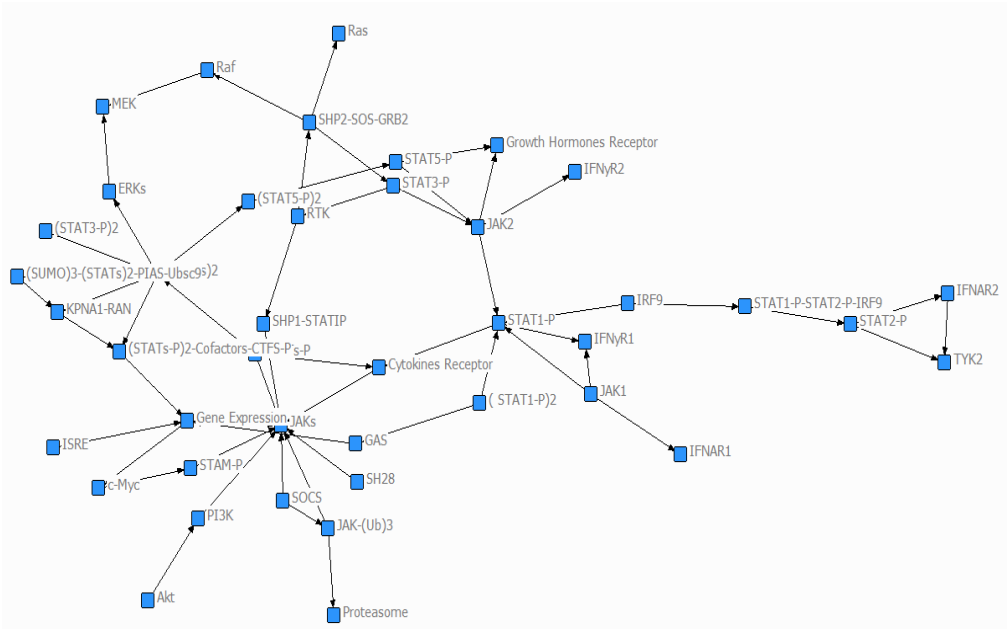

Fig. 4 The network graph of JAK-STAT signaling pathway.

Table 5 Degree of metabolites/reactions in JAK-STAT signaling pathway.

Metabolites/ reactions	Degree	Metabolites/ reactions	Degree	Metabolites/ reactions	Degree	Metabolites/ reactions	Degree
JAK1	3	RTK	3	MEK	2	STAT1-P-STAT2-P-IRF9	2
JAK2	5	IFNAR2	2	PI3K	2	(SUMO)3-(STATs)2-PIAS-Ubsc9	2
TYK2	2	STAT3-P	3	ERKs	2	KPNA1-RAN	3
JAKs	9	STAT1-P	6	Akt	1	GAS	2
SHP1-STATIP	2	STAT2-P	3	STAM-P	2	ISRE	1
Growth Hormones	2	STATs-P	3	c-Myc	2	(STATs-P)2-Cofactors-CTFS-P	3
IFNyR1	2	SH28	1	(STAT5-P)2	2	JAK-(Ub)3	3
STAT5-P	3	SOCS	2	(STAT3-P)2	1	Proteasome	1
IFNyR2	1	SHP2-SOS-GRB2	4	(STAT1-P)2	2	Gene Expression	5
Cytokines Receptor	3	Ras	1	(STATs)2	7		
IFNAR1	1	Raf	2	IRF9	2		

Counted degree of metabolites/reactions is listed in Table 5.

The results showed that *k*-core value of IFNyR2, IFNAR1, SH28, Ras, PI3K, Akt, (STAT3-P)2, ISRE, and Proteasome is 1, and *k*-core value is 2 for remaining metabolites/reactions.

Betweenness centrality of metabolites/reactions showed that JAK2 is the most important metabolite/reaction in JAK-STAT signaling pathway, followed by (STARTs)2, Gene Expression, START5-P and (START5-P)2 (Table 6).

Table 6 Betweenness centrality (BC) of metabolites/reactions in JAK-STAT signaling pathway.

Metabolites/ reactions	BC	Metabolites/ reactions	BC	Metabolites/ reactions	BC	Metabolites/ reactions	BC
JAK1	0	RTK	0.004878	MEK	0	STAT1-P-STAT2-P-IRF9	0.001829
JAK2	0.021951	IFNAR2	0	PI3K	0.00061	(SUMO)3-(STATs)2-PIAS-Ubsc9	0
TYK2	0	STAT3-P	0.009146	ERKs	0.001829	KPNA1-RAN	0.003049
JAKs	0	STAT1-P	0.016768	Akt	0	GAS	0.002134
SHP1-STATIP	0.001829	STAT2-P	0.002439	STAM-P	0.00061	ISRE	0
Growth Hormones	0	STATs-P	0	c-Myc	0.006098	(STATs-P)2-Cofactors-CTFS-P	0.011585
IFNyR1	0	SH28	0	(STAT5-P)2	0.012195	JAK-(Ub)3	0.00061
STAT5-P	0.014634	SOCS	0	(STAT3-P)2	0	Proteasome	0
IFNyR2	0	SHP2-SOS-GRB2	0.007927	(STAT1-P)2	0	Gene Expression	0.015549
Cytokines Receptor	0.003963	Ras	0	(STATs)2	0.019512		
IFNAR1	0	Raf	0.001829	IRF9	0		

3.4 TNF signaling pathway

Fig. 5 is the network graph of TNF signaling pathway.

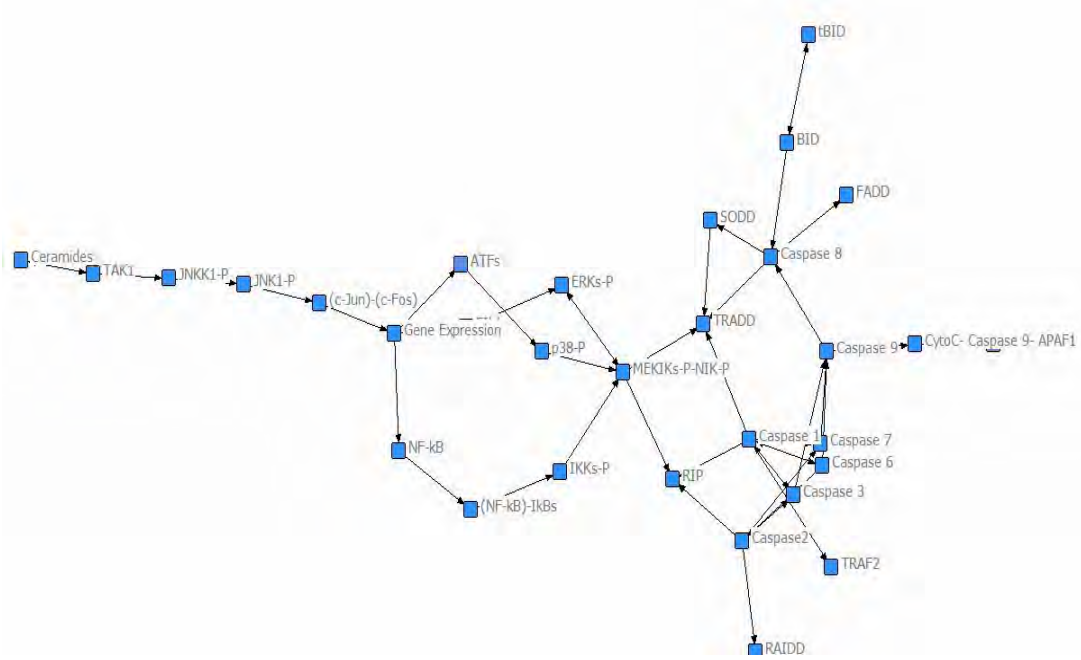

Fig. 5 The network graph of TNF signaling pathway.

Table 7 Degree of metabolites/reactions in TNF signaling pathway.

Metabolites/ reactions	Degree	Metabolites/ reactions	Degree	Metabolites/ reactions	Degree	Metabolites/ reactions	Degree
TRADD	4	Caspase 6	4	Cytoc	2	EIk1	2
SODD	2	Caspase 2	2	IKKs-P	1	Ceramides	1
TRAF2	1	Caspase 7	1	CytoC- Caspase 9-APAF1	2	JNK1-P	2
FADD	1	Caspase 1	2	p38-P	2	JNKK1-P	2
RIP	3	BID	2	(NF-kB)-IkBs	1	TAK1	2
RAIDD	1	Caspase 9	2	ATFs	2	(c-Jun)-(c-Fos)	1
Caspase 3	4	tBID	2	NF-kB	2	Gene Expression	2
Caspase 8	5	MEKIKs-P-NIK-P	2	ERKs-P	1		

Table 8 Betweenness centrality (BC) of metabolites/reactions in TNF signaling pathway.

Metabolites/ reactions	BC	Metabolites/ reactions	BC	Metabolites/ reactions	BC	Metabolites/ Reactions	BC
TRADD	0	Caspase 6	0.009195	Cytoc	0	EIk1	0.017241
SODD	0	Caspase 2	0.006322	IKKs-P	0.011494	Ceramides	0
TRAF2	0	Caspase 7	0.008046	CytoC- Caspase 9-	0.006897	JNK1-P	0.041379
FADD	0	Caspase 1	0.023563	p38-P	0.016092	JNKK1-P	0.029885
RIP	0	BID	0.004598	(NF-kB)-IkBs	0.013793	TAK1	0.016092
RAIDD	0	Caspase 9	0.028736	ATFs	0.017241	(c-Jun)-(c-Fos)	0.050575
Caspase 3	0.008046	tBID	0	NF-kB	0.013793	Gene Expression	0.057471
Caspase 8	0.021839	MEKIKs-P-NIK-P	0.041379	ERKs-P	0.02069		

Counted degree of metabolites/reactions is listed in Table 7.

The results showed that *k*-core value of Caspase 3, Caspase 2, Caspase 6, Caspase 7, Caspase 1, and Caspase 9 is 3, and *k*-core value is 2 or 1 for remaining metabolites/reactions.

Betweenness centrality of metabolites/reactions showed that Gene Expression is the most important metabolite/reaction in TNF signaling pathway, followed by (c-Jun)-(c-Fos), MEKIKs-P-NIK-P and JNK1-P (Table 8).

3.5 Ras signaling pathway

Counted degree of metabolites/reactions is listed in Table 9.

The results showed that *k*-core value of Actin Cytoskeleton, PMA, TCR, and Rho is 1, and *k*-core value is 2 for remaining metabolites/reactions.

Betweenness centrality of metabolites/reactions showed that Ras-GTP is the most important metabolite/reaction in Ras signaling pathway, followed by MEKK1, JNKK and Ras-GDP (Table 10).

Table 9 Degree of metabolites/reactions in Ras signaling pathway.

Metabolites/ reactions	Degree	Metabolites/ reactions	Degree	Metabolites/ reactions	Degree	Metabolites/ reactions	Degree
Integrins	2	RalGDS	3	RalBP1	3	MEKK1	3
Rap1A-GTP	4	MEKs-P	3	PMA	1	Rho	1
PLC-∑	4	Ral	4	CD-GECII	2	p190-B	2
Ras-GDP	7	ERKs-P	3	PI3K	3	JNKK	2
Ras-GTP	16	PLD	2	Rac	5	JNK	3
GRB2	2	ERKs	4	TCR	1	c-Jun-c-Fun	2
GAP	2	CDC42	3	Lck	2	ATF2	2
GEF	2	Elk1	3	PAKs	2	Gene Expression	3
Raf-P	4	ActinCytoskeleton	1	p120-GAP	2		

Table 10 Betweenness centrality (BC) of metabolites/reactions in Ras signaling pathway.

Metabolites/ reactions	BC	Metabolites/ reactions	BC	Metabolites/ reactions	BC	Metabolites/ Reactions	BC
Integrins	0	RalGDS	0.042781	RalBP1	0.003565	MEKK1	0.108734
Rap1A-GTP	0.035651	MEKs-P	0.061497	PMA	0	Rho	0
PLC-∑	0.067736	Ral	0.024955	CD-GECII	0.050802	p190-B	0.008021
Ras-GDP	0.088235	ERKs-P	0.042781	PI3K	0.02139	JNKK	0.090018
Ras-GTP	0.348485	PLD	0	Rac	0.062389	JNK	0.069519
GRB2	0	ERKs	0.024064	TCR	0	c-Jun-c-Fun	0.011141
GAP	0	CDC42	0.002674	Lck	0	ATF2	0.011141
GEF	0	Elk1	0.001783	PAKs	0.026738	Gene Expression	0
Raf-P	0.0918	ActinCytoskeleton	0	p120-GAP	0.016934		

3.6 VEGF signaling pathway (Matsumoto and Claesson-Welsh, 2001)

Counted degree of metabolites/reactions is listed in Table 11.

The results showed that *k*-core value of all metabolites/reactions is 4.

Betweenness centrality of metabolites/reactions showed that ANGIO GENESIS is the most important metabolite/reaction in VEGF signaling pathway, followed by PIP3 and Actin Reorganization (Table 12).

Table 11 Degree of metabolites/reactions in VEGF signaling pathway.

Metabolites/ reactions	Degree	Metabolites/ reactions	Degree	Metabolites/ reactions	Degree	Metabolites/ reactions	Degree
Src	4	Akt/PKB	8	Cell Migration	6	Ca++	4
PIP2	6	p38	4	Cell Suvival	6	ANGIO GENESIS	12
VEGFR2	6	P	4	Ras	4	cPLA	4
PLCy-P	4	MAPKAPK2/3	4	NO production	4	Actin Reorganization	7
MKK3/6	4	BAD-P	6	Raf1	6	Gene Expression	5

PI3K-P	6	HSP27	4	MEK1/2	4	Prostagiandin Production	6
FAK-Paxillin	6	Caspase9-P	6	ERK1/2	6	Vascular Cell Permeability	4
PIP3	6	Focal Adhesion Turnover	4	PKC	4	DAG	6
GRB2-SHC-SOS	4	eNOS-HSP90	4	IP3	6		

Table 12 Betweenness centrality (BC) of metabolites/reactions in VEGF signaling pathway.

Metabolites/ reactions	BC	Metabolites/ reactions	BC	Metabolites/ reactions	BC	Metabolites/ Reactions	BC
Src	0.06634	Akt/PKB	0.108081	Cell Migration	0.106046	Ca++	0.044016
PIP2	0.157028	p38	0.028818	Cell Suvival	0.101791	ANGIO GENESIS	0.336376
VEGFR2	0.120395	P	0.000594	Ras	0.063651	cPLA	0.026292
PLCy-P	0.012032	MAPKAPK2/3	0.055853	NO production	0.035001	Actin Reorganization	0.189037
MKK3/6	0.033571	BAD-P	0.039279	Raf1	0.118018	Gene Expression	0.111727
PI3K-P	0.164617	HSP27	0.091949	MEK1/2	0.07546	Prostagiandin Production	0.085258
FAK-Paxillin	0.11937	Caspase9-P	0.039279	ERK1/2	0.120936	Vascular Cell Permeability	0.081735
PIP3	0.208781	Focal Adhesion	0.069296	PKC	0.065359	DAG	0.094058
GRB2-SHC-SOS	0.060977	eNOS-HSP90	0.017473	IP3	0.067367		

4 Discussion

The results showed that the degree-based relative importance of metabolite/reaction is somewhat different from the betweenness centrality-based relative importance. We adopted the later results. Compared to other signaling pathways, all metabolites/reactions in VEGF signaling pathway have a *k*-core value as high as 4. This means that all metabolites/reactions in VEGF signaling pathway are closely connected.

In this study we did not conduct analysis on undirected networks. Directed networks should be analyzed and more methods and tools should be used to approach tumor signaling pathways in the future (Zhang, 2012a, b).

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